**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| Applicants | : | Schneider et al. |
| Serial No. | : | 09/204,067 |
| Filed | : | March 03, 1998 |
| For | : | **AUTOMATIC LIQUID INJECTION SYSTEM AND METHOD** |
| Group Art Unit: | : | 3734 |
| Examiner | : | LoAn H Thanh |

**DECLARATION UNDER 37 C.F.R. § 1.132**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Laurent Jakob, declare that:

1. I am a citizen of Switzerland residing in Switzerland and one of the five joint inventors of the above identified patent application.

2. I am employed by Bracco Research S.A., the Assignee of the subject patent application, and I've been conducting research in the field of imaging contrast agents and related technologies since 1996, with particular emphasis on medical devices.

3. I am familiar with the content and prosecution of the above identified patent application ('067 application), in particular the Official Action dated April 24, 2002, and with the content of Pokras (US patent no. 5,647,851).

4. Our invention, according to pending claims of in the '067 application, is generally directed to a novel injector system for administering a suspension of microparticles to a patient. Said injection system comprises means for constantly rocking or rotating a syringe, so that the suspension

of microparticles in the syringe is kept homogeneous by preventing segregation of said particles by gravity or buoyancy.

5. I understand from the above cited Official Action that the term "vibration" (referred to the motion applied to the injection device of Pokras for reducing pain when the syringe's needle penetrates the patient's skin) is intended to encompass within its meaning also the rocking and rotating motions as applied to the injector system of the present invention. Based on the above, in the Official Action it is argued that it is inherent that the vibrating injection device disclosed by Pokar will perform the function of preventing segregation of microparticles in a suspension.

6. I have performed comparative experiments to reproduce the device disclosed by Pokras and to determine whether the cited vibrating motion would be capable of preventing segregation of microparticles. To this end, I build up an injection system as illustrated in attached figures 1 and 1a, where the numbers identifying the different parts of the system correspond to the respective parts of fig. 6 of Pokras. As for the injection system disclosed by Pokras, the injection system of figure 1 comprises a motor 28, with an eccentrically weighted shaft 30, fixed on the side of the supporting plate16, to cause the syringe to vibrate and transmit the desired vibration motion to a needle attached to said syringe. Incidentally, I remark an apparent inconsistence between the description and the claims of Pokras; in the description, a rotation of the motor of about 60 rpm (or cycles per minutes) is in fact disclosed (col 8, line 46), whereby in claim 11 a vibration of 60 cycles per second is claimed. Both rotation frequencies have thus been exploited in the comparative experiments. The injection system illustrated in figure 1 further comprises a motor M for the transmission of a rocking/rotating motion to the syringe according to the present invention. When the comparative experiments without any motion or with the only vibration described by Pokras were carried out, the motor M was disconnected from the syringe. In addition, the exit of the syringe was connected to a tube T, which was in turn connected to a Coulter counter (Beckman Coulter Multisizer II) to monitor the concentration of microbubbles in the suspension exiting from the

syringe during the tests (infusion rate: 0.5 ml/min for 35 min). The syringe was a B.BRAUN Original-Perfusor®-Spritze OPS 20 mL Luer Lock, while the exit tube was a Sidam PVC extension tube (int. diameter, 0.5 mm). Microbubble suspensions were obtained from reconstituted vials of SonoVue™ (Bracco Imaging BV).

7. The enclosed figure 2 shows a graph reporting the results of the experiment. The graph illustrates the variation of the concentration of microbubbles in the suspension as a function of infusion time. The concentration at each time is defined as the percentage of the counted number of microbubbles with respect to the number of microbubbles as determined in the initial reconstituted suspension. Curve A shows the result of an infusion carried out according to the present invention, by applying a rocking motion to the syringe of 30 cycles per minutes, the rotation of the syringe being reversed at 270°. Curve B shows the result of a perfusion carried out without any motion applied to the syringe. Curve C shows the result of a perfusion carried out by applying a vibrating motion to the syringe, generated by a rotation of 60 cycles per minute of motor 28. Curve D shows the result of a perfusion carried out by applying a vibrating motion to the syringe, generated by a rotation of 60 cycles per second of motor 28.

8. As shown in figure 2, by applying a rocking motion according to the invention, a substantial constant concentration of microbubbles in the infused suspension is observed during the whole infusion test. On the contrary, the vibration generated by motor 28 according to Pokras is not capable of avoiding segregation of microbubbles, curves C and D being substantial identical to the curve obtained without applying any motion to the syringe. All these curves (B, C and D) show that, due to the increasing segregation of microbubbles in the upper portion of the syringe, the concentration of microbubbles flowing from the central part of the syringe through the exit tube is continuously decreasing during the test.

9. I HEREBY DECLARE that all statements made herein are of my own knowledge and are true, and that all statements made on information and belief are believed to be true; and

further that the statements have been made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of any patents issuing on the present application.

Respectfully submitted,

Dated: 14/04/2003 By: [signature]

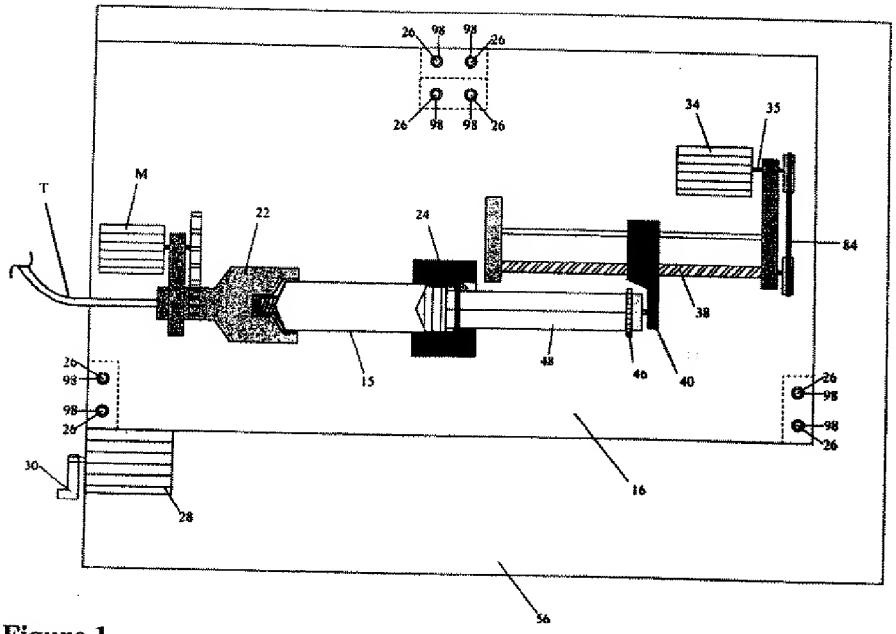


**Figure 1**

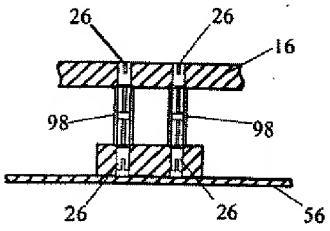


**Figure 1a**

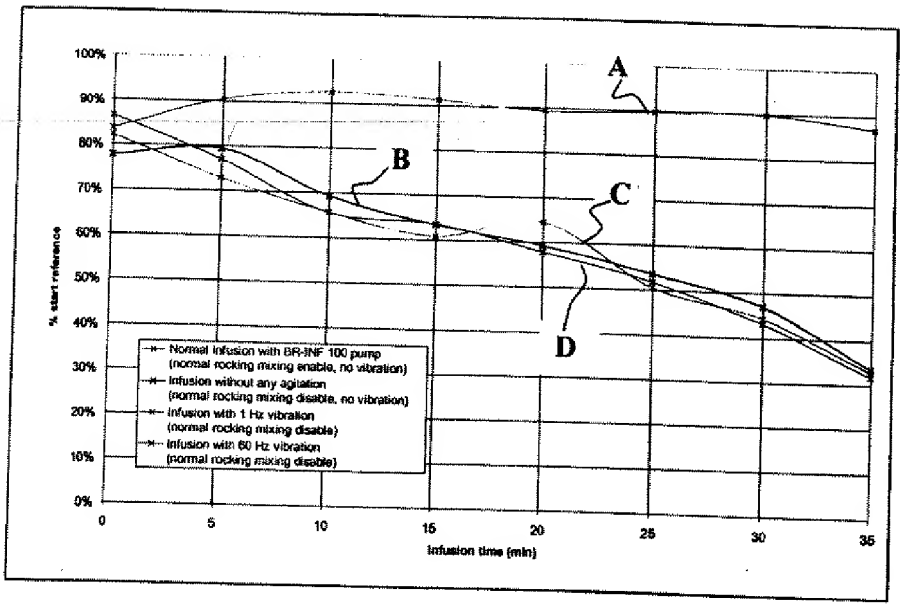
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% start reference
0
5
10
15
20
25
30
35
Infusion time (min)
A
B
C
D
Normal infusion with BR-INF 100 pump (normal rocking mixing enable, no vibration)
Infusion without any agitation (normal rocking mixing disable, no vibration)
Infusion with 1 Hz vibration (normal rocking mixing disable)
Infusion with 60 Hz vibration (normal rocking mixing disable)

**FIGURE 2**